



Australian Government

Medical Services Advisory Committee

## Public Summary Document

### **Application No. 1617 – BRAF V600 testing to help determine eligibility for PBS access to Braftovi (encorafenib), in patients with metastatic colorectal cancer (Stage IV)**

**Applicant:** Pierre Fabre Australia Pty Ltd

**Date of MSAC consideration:** MSAC 81<sup>st</sup> Meeting, 31 March – 1 April 2021

Context for decision: MSAC makes its advice in accordance with its Terms of Reference, [visit the MSAC website](#)

#### **1. Purpose of application**

The integrated codependent submission received from Pierre Fabre Australia Pty Ltd by the Department of Health in November 2020 was an integrated codependent application for:

- Inclusion of B-rapidly accelerated fibrosarcoma (*BRAF*) V600E testing into the existing Medicare Benefits Schedule (MBS) item 73338 (listing for rat sarcoma oncogene (*RAS*) testing for metastatic colorectal cancer (mCRC)) for the evaluation of *BRAF* V600E variant to determine eligibility for treatment with encorafenib in combination with an epidermal growth factor receptor (EGFR) inhibitor, such as cetuximab, in patients with *BRAF* V600E variant mCRC; and
- Pharmaceutical Benefits Scheme (PBS) Streamlined Authority Required listing of encorafenib in combination with an existing PBS-listed EGFR inhibitor, such as cetuximab for the treatment of mCRC in patients who have evidence of the *BRAF* V600E variant, and who have received prior systemic therapy.

The submission flagged a note on the terminology used, that as per the Human Genome Variation Society (HGVS) recommendations (den Dunnen et al. 2016), the term ‘variant’ should be used to replace the term ‘mutation’; and ‘*BRAF* V600E’ pathogenic variant refers to both class 4 (likely pathogenic) and class 5 (known pathogenic) variants. This is similar for *RAS* and other pathogenic variants.

#### **2. MSAC’s advice to the Minister**

After considering the strength of the available evidence in relation to comparative safety, clinical effectiveness and cost-effectiveness, MSAC supported an amendment to the descriptor for Medicare Benefits Schedule (MBS) item 73338 to include *BRAF* V600 testing, noting that this amendment would not be associated with any change in the fee for this item.

## MSAC-recommended MBS listing

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|---|
| Category 6 – Pathology Services   |
| MBS item 73338<br>A test of tumour tissue from a patient with metastatic colorectal cancer (stage IV), requested by a specialist or consultant physician, to determine if:<br><br>1. requirements relating to rat sarcoma oncogene ( <i>RAS</i> ) gene variant status for access to cetuximab or panitumumab under the Pharmaceutical Benefits Scheme (PBS) are fulfilled, if:<br>(a) the test is conducted for all clinically-relevant variants on <i>KRAS</i> exons 2, 3 and 4, and <i>NRAS</i> exons 2, 3, and 4; or<br>(b) a clinically-relevant <i>RAS</i> variant is detected;<br><br>and, in cases where no <i>RAS</i> variant is detected<br><br>2. the requirements relating to <i>BRAF</i> V600 gene variant status for access to encorafenib under the Pharmaceutical Benefits Scheme (PBS) are fulfilled. |
| Fee: MBS Fee: \$362.60 Benefit: 75% = \$271.95 85% = \$308.25   |

### Consumer summary

Pierre Fabre Australia Pty Ltd has submitted an integrated codependent submission to the Medical Services Advisory Committee (MSAC) and the Pharmaceutical Benefits Advisory Committee (PBAC). The MSAC application is for funding through the Medicare Benefits Schedule (MBS) of *BRAF* V600 genetic testing for people with metastatic colorectal cancer (stage IV bowel cancer that has spread to other areas of the body). The PBAC application is for funding through the Pharmaceutical Benefits Scheme (PBS) of a medicine called encorafenib for people who test positive to the *BRAF* V600 variant.

People with stage IV bowel cancer and with a *BRAF* V600 variant have a low survival rate and their cancer spreads quickly. When treated with the drug encorafenib, these people survive longer and have better quality of life.

There are different variants of *BRAF* V600. V600E is the most common. MSAC considered that all variants might respond to encorafenib, and found no reason to just test for a specific V600 variant.

The applicant suggested that *BRAF* V600 genetic testing be added to an existing MBS item (73338) which funds testing for *RAS* gene variants. Many laboratories are already testing for *BRAF* gene status when they are testing a tumour for *RAS* gene status. This application requested testing for *BRAF* status if the *RAS* gene test is negative, without changing the MBS rebate for *RAS* testing. It is very rare for people to have variants in both the *RAS* gene and the *BRAF* gene. Therefore, MSAC considered that people who have a *RAS* variant do not need to be tested for *BRAF* V600 variants.

### MSAC's advice to the Commonwealth Minister for Health

MSAC recommended that *BRAF* V600 genetic testing be funded for people with metastatic bowel cancer. MSAC considered the test to be safe, effective and cost-effective. MSAC considered it appropriate to test for all *BRAF* V600 variants for access to encorafenib. MSAC also considered that people with variants in their *RAS* gene did not need to undergo *BRAF* testing as well.

### 3. Summary of consideration and rationale for MSAC's advice

MSAC noted that this was a codependent application for MBS listing of *BRAF* V600E test in metastatic colorectal cancer (mCRC) for access to encorafenib (*BRAF* inhibitor) on the Pharmaceutical Benefits Scheme (PBS). MSAC noted that the Pharmaceutical Benefits Advisory Committee (PBAC) deferred its consideration of encorafenib until an MSAC intention to support the codependent *BRAF* V600 testing in mCRC via the MBS is available. MSAC further noted that the PBAC foreshadowed its support for recommending that encorafenib in combination with cetuximab be listed and stated that, if MSAC subsequently decided to support the MBS listing of *BRAF* V600 testing in mCRC, it would support an expedited process for reconsideration to align any PBAC recommendation for listing encorafenib aligned with the circumstances supported by MSAC.

MSAC noted that the *BRAF* V600E variant increases the risk of mortality (hazard ratio = 4.24; 95% CI: 1.77, 10.2 in the only prospective cohort study) and disease progression in patients with mCRC. MSAC noted that treatment options for patients with pathogenic *BRAF* variants are limited, thus acknowledging the high clinical need for effective treatment options. MSAC noted that the BEACON trial showed that, in patients with mCRC and the *BRAF* V600E variant, encorafenib plus cetuximab significantly improved overall survival compared with cetuximab plus chemotherapy (stratified hazard ratio **redacted** (95% CI: **redacted** to **redacted**, 5 May 2020 data cut)<sup>1</sup>. Compared with cetuximab plus chemotherapy, encorafenib plus cetuximab also improved the overall response rate and progression-free survival (PFS), and produced manageable tolerability and sustained quality of life (QoL).

However, MSAC also noted that the BEACON trial only enrolled patients with the V600E variant, and so could not assess the effect for patients who are V600 negative or had another V600 variant. Therefore, MSAC considered that the rationale for codependency was based on biological plausibility and on preclinical studies, which have not shown that encorafenib is effective against *BRAF* V600 wild-type tumours.

MSAC further considered that it is biologically plausible for other *BRAF* V600 variants to respond similarly to encorafenib. MSAC recalled that, in melanoma, other *BRAF* V600 variants are considered actionable with documented response to encorafenib (Public Summary Document [PSD] Application No. 1543, p3).

MSAC noted that the literature states that *BRAF* V600E accounts for >90% of the *BRAF* variants found in CRC, with a suggestion that other *RAS*-independent V600[x] variants might behave similarly, along with rare variations in codons 601 and 597 (Yao *et al.* 2017)<sup>2</sup>. MSAC acknowledged that a small number of patients with these V600E-like variants will not be eligible for treatment under the proposed PBS and MBS listings although not all assays in current use in Australia will distinguish between different V600 variants or detect non-V600 variants (for example the Idylla *NRAS/BRAF* kit only detects V600 variants and does not distinguish between them). MSAC also noted that Class 3 *RAS*-dependent *BRAF* variants also rarely occur in *BRAF* codons 546 and 596 (Schirripa *et al.* 2019)<sup>3</sup>. These tumours are often well-differentiated and, prognosis-wise, behave more like *BRAF* wild-type tumours. MSAC noted that the *BRAF* V600 testing looks for variants resulting in changes at codon 600 of the

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<sup>1</sup> OS data cut off May 2020: manuscript in preparation. To be submitted Q3 2021 to BMJ Open

<sup>2</sup> Yao Z *et al.* Tumours with class 3 BRAF mutants are sensitive to the inhibition of activated RAS. *Nature*. 2017;548(7666):234-238.

<sup>3</sup> Schirripa *et al.* Clinico-pathological and molecular characterisation of BRAF mutant metastatic colorectal cancer (mCRC): Are all mutations created equal? [abstract] *Journal of Clinical Oncology* 2018 36:15\_suppl, 3590-3590

BRAF protein. MSAC considered that variants on other codons (eg 546, 596) may change the shape of the tyrosine kinase pocket that is targeted by encorafenib and thus reduce its efficacy. MSAC thus concluded that the inability to detect these variants in assays that only assess V600 is unlikely to be a problem.

MSAC therefore supported testing for all V600 variants, and considered that testing should not be limited to V600E. MSAC also noted that, for melanoma, testing is not restricted to the V600E variant. MSAC acknowledged that this may be different to the indication approved by the Therapeutic Goods Administration (TGA).

MSAC noted that patients with mCRC are routinely assessed for *RAS* status, but that it is extremely rare to be both *RAS* positive and *BRAF* V600 positive. MSAC noted that many laboratories also assess *BRAF* status at the same time as part of the *RAS* assessment. However, MSAC noted that *BRAF* testing is not required if *RAS* status is positive.

MSAC advised that not all *RAS/BRAF* testing in Australia is currently being done by next-generation sequencing (NGS) panels, as stated in the application. MSAC noted that some pathology providers use sequential polymerase chain reaction (PCR) testing. MSAC noted that laboratories using NGS will simultaneously test for *RAS* and *BRAF* variants whereas laboratories using PCR may first test *KRAS* then test for *NRAS* and *BRAF* V600 if *KRAS* is wild-type.

MSAC noted that no reference standard was presented for detecting the *BRAF* V600E variant, but noted that the BEACON bridging study between the clinical trial assay and the subsequently marketed assay reported high (>99%) concordance and a similar prediction of encorafenib's reduction in mortality. Other analytical concordance studies across different *BRAF* testing methodologies reported good (between >95% and >99%) concordance. MSAC therefore agreed with the pre-MSAC response that the concordance was high and the lack of a reference standard was not of concern for decision making. MSAC concluded that the item therefore did not need to specify any particular testing methodology.

MSAC noted the commentary's sensitivity analyses of test accuracy (assuming 5% misclassification as worst-case scenario) shows a 5.3% increase on the incremental cost-effectiveness ratio (ICER). MSAC considered this to support the value of the accuracy of the test.

MSAC noted advice from the National Pathology Accreditation Advisory Council (NPAAC) that *BRAF* testing is established with a quality assurance program (QAP) provided through the Royal College of Pathologists of Australasia (RCPA). MSAC noted that the RCPA was proposing to include *BRAF* V600 testing in its existing colorectal cancer QAP.

MSAC noted that including the requirement for *BRAF* testing is not proposed to change the cost of current *RAS* testing or its utilisation, with no increased cost to the MBS. MSAC considered whether individual laboratories would increase their fees if *BRAF* was included and thus result in out-of-pocket costs, but found no evidence to support this. MSAC considered that repeat testing should not be restricted as repeat testing using a different method may be needed for a small number of cases with indeterminate results. MSAC noted that 3% of patients accessing item 73338 between 2014 and 2017 received two or more services. MSAC considered that the proposed item descriptor would require the requesting clinician to make another request and did not consider this to be necessary. Overall, MSAC supported funding *BRAF* V600 testing in mCRC, subject to the following item descriptor changes to the current MBS item 73338 (after point 1b and *in italics*):

A test of tumour tissue from a patient with metastatic colorectal cancer (stage IV), requested by a specialist or consultant physician, to determine if:

- 1) requirements relating to rat sarcoma oncogene (RAS) gene variant status for access to cetuximab or panitumumab under the Pharmaceutical Benefits Scheme (PBS) are fulfilled, if:
  - a) the test is conducted for all clinically-relevant variants on KRAS exons 2, 3 and 4, and NRAS exons 2, 3, and 4; or
  - b) a clinically-relevant RAS variant is detected;

... and, in cases where no RAS variant is detected

- 2) the requirements relating to *BRAF* V600 gene variant status for access to encorafenib under the Pharmaceutical Benefits Scheme (PBS) are fulfilled.

MSAC's support is also subject to TGA approval and PBAC support for listing encorafenib.

#### 4. Background

The MSAC has not previously considered *BRAF* V600E testing for access to encorafenib for mCRC. The ADAR (p19) noted that within pathogenic *BRAF*-variants in mCRC, *BRAF* V600E accounts for more than 90% (Luu and Price, 2019)<sup>4</sup>.

##### *Application 1543*

*BRAF* V600 testing is currently MBS listed via MBS item 73336 as a means of determining eligibility for PBS-listed encorafenib for the treatment of patients with metastatic melanoma. The COLUMBUS trial, considered by MSAC in its November 2018 consideration of *BRAF* V600 testing to determine eligibility for encorafenib in metastatic melanoma, used the BioMerieux THxIDTM *BRAF* diagnostic test that can identify both *BRAF* V600E and V600K gene variants to select patients eligible for the study ([Public Summary Document \[PSD\] Application No. 1543](#), p3).

##### *Application 1207*

In April 2013, MSAC considered *BRAF* V600 testing for locally advanced or metastatic melanoma to determine eligibility for dabrafenib treatment. The submission presented response rates from the single-arm Phase II BREAK-2 study. It stated these results provide evidence that patients whose tumours harbour non-V600E (including *BRAF* V600K) mutations derive clinical benefit from dabrafenib consistent with that observed in patients with *BRAF* V600E-positive melanomas ([PSD Application 1207](#), p4). The eligible population for the BREAK-3 trial was limited to those with *BRAF* V600E-positive melanoma ([PSD Application 1207](#), p4-5).

##### *Application 1172*

In August 2012, MSAC considered application 1172 for *BRAF* testing in patients with unresectable stage III or metastatic stage IV melanoma to determine eligibility for vemurafenib treatment. MSAC discussed whether the definition of the biomarker should be limited to V600E mutations (as prespecified for BRIM3), to V600E or V600K mutations (noting that BRIM3 also randomised participants with V600K mutations – because the Cobas 4800 assay used in BRIM3 trial has some cross reactivity with V600K – and reported results for this subgroup), or to any V600 mutation. MSAC noted that the limited prevalence data

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<sup>4</sup> Luu LJ, Price JT. *BRAF* mutation and its importance in colorectal cancer. *Adv. Mol. Underst. Color. Cancer*. 2019 Jan 17:1-8.

available suggested that V600K may be more prevalent in Australia than in BRIM3 and that this might be explained by the exclusion of patients with brain metastases from BRIM3 and the greater rate of melanoma associated with sun exposure in Australia ([PSD Application 1172](#), p9).

In the context of a more general set of issues to be considered when judging the optimal definition of the biomarker as had been recorded in its deliberations relating to [application 1173](#) (*EGFR* testing to support first-line erlotinib), MSAC advised that the biomarker be defined simply as “*BRAF* V600 mutations”. It based this advice on the non-statistically significant trend towards a greater treatment effect in the exploratory analysis of the 57/675 (8%) participants in BRIM3 with V600K mutations and the rarity of other V600 mutations meaning that evidence of harm or benefit cannot be concluded from the 18/675 (3%) participants in BRIM3 who had neither a V600E nor a V600K mutation. In the absence of clear clinical utility data for the residual V600 mutation subtypes, MSAC accepted expert advice that there was *in vitro* data to support a conclusion that the other mutation subtypes also drive melanoma growth, and that a *BRAF* inhibitor stops this growth. In addition, MSAC accepted that there was a biological argument that these subtypes all have the same functional consequences and similar three-dimensional structure.

MSAC supported the addition of vemurafenib to MBS Item 73336 at its March 2016 meeting ([PSD Application 1172.1](#)).

## **5. Prerequisites to implementation of any funding advice**

The submission stated that no specific test type is requested for *BRAF* V600E testing, and that existing testing panel approaches used for MBS item 73338, currently used for the determination of pathogenic genetic variants in mCRC tumours, could be used if they include the *BRAF* V600E test. All MBS-billable *BRAF* V600E tests must occur in National Association of Testing Authorities (NATA) accredited laboratories utilising Therapeutic Goods Australia (TGA) listed test kits. Competence to perform the requested test currently listed in MBS item 73336 (*BRAF* V600 testing) is already being monitored through a Royal College of Pathologists Australasia (RCPA) quality assurance program (QAP). The National Pathology Accreditation Advisory Council (NPAAC) advised that *BRAF* V600E testing is already established in a number of laboratories in Australia.

## **6. Proposal for public funding**

The submission requested that *BRAF* V600E testing be added to the current descriptor for MBS item 73338 to determine eligibility for PBS-listed encorafenib. MBS item 73338 allows testing for *RAS* status of a patient with mCRC to determine eligibility for PBS-listed cetuximab or panitumumab. The submission did not propose a change to the applicable fee for the test as it is currently routinely performed and reported alongside *RAS* status as an important prognostic tool. The Commentary considered that this was reasonable. The Commentary highlighted that the submission does not consider any additional out-of-pocket costs that may be incurred by patients due to the inclusion of the formal reporting of *BRAF* V600E testing as part of MBS Item 73338. The proposed new descriptor for MBS item 73338 is presented in Table 1. This was consistent with the proposed MBS item descriptor agreed in the ratified PICO confirmation. The requested test intervention, *BRAF* V600E test, and the eligible population, were consistent with those specified in the ratified PICO confirmation.

**Table 1 Proposed MBS listing**

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|--|
| Category 6 – Pathology Services  |
| <b>MBS item 73338</b><br>A test of tumour tissue from a patient with metastatic colorectal cancer (stage IV), requested by a specialist or consultant physician, to determine if:<br><br>requirements relating to rat sarcoma oncogene ( <i>RAS</i> ) gene variant status for access to cetuximab or panitumumab under the Pharmaceutical Benefits Scheme (PBS) are fulfilled, if:<br>(a) the test is conducted for all clinically-relevant variants on <i>KRAS</i> exons 2, 3 and 4, and <i>NRAS</i> exons 2, 3, and 4; or<br>(b) a clinically-relevant <i>RAS</i> variant is found;<br><br><i>and, when also requested</i><br><br><i>requirements relating to BRAF V600E gene variant status for access to encorafenib under the Pharmaceutical Benefits Scheme (PBS) are fulfilled.</i> |
| Fee: MBS Fee: \$362.60 Benefit: 75% = \$271.95 85% = \$308.25  |

Note: *italicised is the proposed additional descriptor for MBS item 73338 to formalise the inclusion of BRAF V600E in the gene panel reporting for access to encorafenib under the PBS.*

Abbreviations: *BRAF* = B-Rapidly Accelerated Fibrosarcoma; *KRAS* = Kirsten Rat Sarcoma Oncogene; *NRAS* = Neuroblastoma Rat Sarcoma Oncogene; *RAS* = Rat Sarcoma Oncogene; PBS = Pharmaceutical Benefits Scheme.

Source: Table 1-14, p53 of the submission.

## **7. Summary of public consultation feedback/consumer issues**

No consumer feedback/consumer comments were received for this application.

## **8. Proposed intervention's place in clinical management**

A summary of the components of the overall clinical claim addressed by the submission is presented in Table 2. While the submission stated that the proposed pharmaceutical intervention was 'treatment with encorafenib in combination with an EGFR inhibitor such as cetuximab' it presented clinical evidence to support only the effectiveness and safety of encorafenib + cetuximab and not encorafenib in combination with any other EGFR inhibitor, such as the currently available panitumumab.

**Table 2 Key components of the clinical issue addressed by the submission**

| Component      | Description  |
|----------------|--|
| Population     | Test: Patients diagnosed with Stage IV metastatic colorectal cancer (mCRC).<br>Medicine: Patients with mCRC who have received prior systemic therapy in the metastatic setting, and who have a <i>BRAF</i> V600E pathogenic variant in tumour tissue. <sup>a</sup>   |
| Intervention   | Test: <i>BRAF</i> V600E variant testing added to existing MBS item 73338.<br><i>BRAF</i> V600E variant testing <sup>b</sup> involves taking a biopsy of the mCRC tumour and performing DNA extraction and assay. <sup>c</sup><br>Medicine: Treatment with encorafenib [in combination with an EGFR inhibitor such as cetuximab] (also known as a doublet-therapy group). <sup>d</sup>  |
| Comparator     | Test: No testing, i.e. MBS item 73338 in its current format, which has no explicit inclusion of <i>BRAF</i> V600E variant testing in mCRC, and no reference to encorafenib.<br>Medicine: FOLFIRI + cetuximab or irinotecan + cetuximab.  |
| Outcomes       | Test: Concordance between the evidentiary standard and other <i>BRAF</i> V600E variant testing methods likely to be used in Australia.<br>Medicine: OS, ORR, PFS, health-related quality of life and adverse events associated with treatment.   |
| Clinical claim | Test: <i>BRAF</i> V600E variant testing methods likely to be used in Australia are concordant.<br>Medicine: Encorafenib in combination with an anti-EGFR agent such as cetuximab <sup>d</sup> , is superior in terms of effectiveness compared with FOLFIRI + cetuximab or irinotecan + cetuximab.<br>Encorafenib in combination with an anti-EGFR agent such as cetuximab <sup>d</sup> , demonstrated a manageable tolerability profile and is superior in terms of safety compared with FOLFIRI + cetuximab or irinotecan + cetuximab. |

Source: Table 1-1, p 23-24 of the submission.

Abbreviations: BRAF = B-rapidly accelerated fibrosarcoma; EGFR = epidermal growth factor receptor; FOLFIRI = 5-fluorouracil/folinic acid/irinotecan; FOLFOX = 5-fluoracil/folinic acid/oxaliplatin; MBS = Medicare Benefits Schedule; mCRC = metastatic colorectal cancer; ORR = objective response rate; OS = overall survival; PFS = progression-free survival.

<sup>a</sup> Key exclusion criteria included no prior treatment with any rapidly accelerated fibrosarcoma (RAF) inhibitor, mitogen-activated protein kinase (MEK) inhibitor, cetuximab, panitumumab or other EGFR inhibitors.

<sup>b</sup> Upon the amendment of MBS item 73338, to include *BRAF* V600E testing alongside *RAS* gene testing.

<sup>c</sup> Such as polymerase chain reaction (PCR) based assays, Sanger sequencing, or next generation sequencing (NGS).

<sup>d</sup> The clinical evidence in support of the effectiveness and safety was based on information for encorafenib + cetuximab and not in combination with any other EGFR inhibitor (such as panitumumab).

The submission stated that approximately 50% of new patients with CRC (stage I, II, III) will progress to mCRC during the course of their disease. Of mCRC patients, approximately 55% are *RAS* wild type and 45% have a *RAS* pathogenic variant. The *BRAF* variant, a sub-category of *RAS* wild type, is a different pathogenic genetic variant, and accounts for around 10% of patients with mCRC in clinical trials. Within *BRAF* pathogenic variants in mCRC, *BRAF* V600E accounts for 90-95% of all *BRAF* variants. Other *BRAF* variants include V600K, V600R and V600D. The submission noted that the *BRAF* V600 variants occur in approximately 10-13% of Australian mCRC patients.

The target population for the *BRAF* V600E genetic test is all patients newly diagnosed with mCRC. The biomarker, the *BRAF* V600E variant, where a valine-to-glutamate change occurs at position 600, is characterised by increased kinase activity in the BRAF protein, a constituent in the EGFR-mediated MAPK pathway. Compared to other mCRC subtypes, the presence of the *BRAF* V600E variant indicates poor prognosis.

In order to detect the presence of the *BRAF* V600E variant, the test involves taking a biopsy of the mCRC tumour (often done by the surgeon or oncologist who requests testing) and performing DNA extraction and assay. The procedure is similar to conducting *RAS* testing in patients with mCRC, as prescribed in MBS item 73338, and the same as conducting *BRAF* V600E testing in patients with metastatic melanoma, as prescribed in MBS item 73336. Examples of assays include next generation sequencing (NGS), polymerase chain reaction (PCR), mass spectrometry (MS), high resolution melting (HRM) and Sanger sequencing.

The proposed gene testing and treatment pathways for patients with mCRC were based on current diagnostic and treatment pathways for mCRC in the Australian healthcare system. The submission claimed that once mCRC is diagnosed, a patient's surgeon or oncologist would ordinarily order *BRAF* V600E testing which is conducted at the same time as *RAS* testing under MBS item 73338. The presence of a *RAS* pathogenic variant, as opposed to being *RAS* wild type, rules out the presence of a *BRAF* pathogenic variant. Those with *RAS* wild type could have either *BRAF* wild type or *BRAF* variants, as depicted in the current treatment regimen. The submission noted that given that determination of *BRAF* status can be conducted as part of existing testing procedures, the expansion of MBS item 73338 would not necessitate investment in specific equipment required for its performance. This was considered reasonable by the Commentary and supported by the survey of pathologists presented in the submission. The proposed testing was consistent with the proposed treatment pathway.

The submission claimed that there is no reference standard available for the current testing methodologies for the *BRAF* V600E variant. The Commentary noted that no justification was provided by the submission to support this claim. The Commentary noted that [MSAC Application 1172](#) (*BRAF* genetic testing in patients with metastatic melanoma) proposed a reference standard constructed using DNA sequencing (Sanger sequencing) with confirmatory pyrosequencing for the resolution of discordant cases. This reference included all *BRAF* V600 pathogenic variants rather than the *BRAF* V600E variant specified in the current submission. The Commentary noted that although DNA sequencing has previously been considered the reference standard in *BRAF* V600 testing, it is not 100% sensitive or specific (Cheng et al. 2018)<sup>5</sup>. More recently next-generation sequencing (NGS) testing has been considered as an alternative reference standard (Lo et al. 2016)<sup>6</sup>.

The theascreen<sup>®</sup> real time (RT)-polymerase chain reaction (PCR) companion diagnostic (CDx) Kit, hereafter referred to as RT-PCR-CDx test was nominated by the submission as the evidentiary standard. The submission justified this choice by arguing the similarity between CDx and theascreen<sup>®</sup> RT-PCR clinical trial assay (CTA) Kit, hereafter referred to as RT-PCR-CTA, which was used in the pivotal trial BEACON CRC (hereafter referred to as BEACON) for the proposed PBS listing to establish the presence of the *BRAF* V600E variant. RT-PCR-CDx has additional software changes compared to RT-PCR-CTA. The Commentary noted that the implications, if any, of those additional software changes were not addressed by the submission, however the submission presented a bridging study which estimated the concordance between RT-PCR-CDx and RT-PCR-CTA.

## 9. Comparator

The proposed test comparator is MBS item 73338 with its current item, which allows testing for *RAS* status of a patient with mCRC to determine eligibility for cetuximab or panitumumab. The Commentary considered that this was appropriate.

## 10. Comparative safety

The approach taken in the submission to support the contention that targeting of *BRAF* V600E with encorafenib + cetuximab will improve patients' overall survival (OS),

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<sup>5</sup> Cheng L, Lopez-Beltran A, Massari F, MacLennan GT, Montironi R. Molecular testing for BRAF mutations to inform melanoma treatment decisions: a move toward precision medicine. *Mod Pathol*. 2018;31(1):24-38.

<sup>6</sup> Louisa Lo, Timothy Price, Joanne Young and Amanda Townsend (September 7th 2016). *BRAF Mutation in Colorectal Cancer, Colorectal Cancer - From Pathogenesis to Treatment*, Luis Rodrigo, IntechOpen, DOI: 10.5772/62226. Available from: <https://www.intechopen.com/books/colorectal-cancer-from-pathogenesis-to-treatment/braf-mutation-in-colorectal-cancer>

progression-free survival (PFS) and overall response rate (ORR), and sustain their quality of life (QoL) was to present a linked evidence approach, as summarised in Table 3.

**Table 3 Summary of the linked evidence approach**

|  | Type of evidence supplied   | Extent of evidence supplied  | Overall risk of bias in clinical trials |
|--|---|--|---|
| Accuracy and performance of the test (analytical validity) | 1 diagnostic case control study<br>15 concordance studies   | <input checked="" type="checkbox"/> k=1 n=600<br><input checked="" type="checkbox"/> k=15 n= 3,268 | Low<br>Moderate                         |
| Prognostic evidence  | 1 prospective cohort study<br>17 retrospective cohort studies   | <input checked="" type="checkbox"/> k=1 n=139<br><input checked="" type="checkbox"/> k=17 n= 5,061 | Moderate                                |
| Change in patient management                               | No evidence provided  | <input type="checkbox"/> k=0 n=0   |   |
| Treatment effectiveness                                    |   |  |   |
| Predictive effect (treatment effect variation)             | No evidence provided  | <input type="checkbox"/> k=0 n=0   |   |
| Treatment effect (enriched)                                | Single randomised controlled trial of encorafenib + cetuximab compared to irinotecan/cetuximab or FOLFIRI/cetuximab in patients with <i>BRAF</i> V600E positive mCRC. | <input checked="" type="checkbox"/> k=1 n=441  | Low                                     |

Abbreviations: BRAF= B-Rapidly Accelerated Fibrosarcoma; FOLFIRI = 5-fluorouracil/ folinic acid/irinotecan; k=number of studies, mCRC = metastatic colorectal cancer; n=number of patients.

Source: constructed during the evaluation.

The submission presented evidence to address some parts of the analytic framework as outlined in Table 4. No evidence was presented to inform the following comparisons:

- *BRAF* V600E test versus no *BRAF* V600E test
- *BRAF* V600E test versus an alternative test
- outcomes for patients who tested negative to *BRAF* V600E in the proposed medicine arm versus patients who tested negative to *BRAF* V600E in the comparator medicine arm.

**Table 4 Data availability to inform comparisons**

|                                   |  |                      |
|-----------------------------------|--|----------------------|
| Proposed test vs no test          | No evidence presented                            |                      |
| Proposed test vs alternative test | Concordance of all available tests was presented |                      |
|                                   | Proposed medicine                                | Comparator medicine  |
| Biomarker test positive           | BEACON   | BEACON               |
| Biomarker test negative           | No evidence presented                            | No evidence provided |

Source: constructed during the evaluation.

The patient populations varied across the linked evidence, including advanced or mCRC versus more specific populations such as non-resectable mCRC. Patient characteristics such as *BRAF* V600E status varied across studies. Studies did not always report the *BRAF* pathogenic variant nor the *BRAF* pathogenic variant status. *BRAF* V600E testing methodology and treatments varied across the linked evidence. *BRAF* V600E testing methodologies included pyrosequencing, NGS, RT-PCR, direct sequencing, Sanger sequencing and bidirectional sequencing. Treatments included tumour resection, thoracic procedure, anti-EGFR treatment, bevacizumab treatment and systemic chemotherapy.

The Commentary considered the overall risk of bias was moderate for studies assessing the prognostic effect of a *BRAF* V600E variant and the accuracy and performance of *BRAF* V600E tests.

The key clinical evidence presented by the submission to support the comparative effectiveness and safety of encorafenib + cetuximab, compared to irinotecan/cetuximab or FOLFIRI/cetuximab, was from BEACON. The Commentary considered the overall risk of bias in BEACON was low, noting the following as potential sources of bias:

- The Phase 3 Response Efficacy Set consisted of the first 331 patients randomised (n = 111 encorafenib + binimetinib + cetuximab arm; n = 113 encorafenib + cetuximab arm and n = 107 control arm) to ensure patients had sufficient follow-up of at least 9 months (p7 BEACON Addendum Clinical Study Report 15 Aug 2019) and not from the full analysis set (FAS) (N = 665). The results for objective tumour response rates at the primary analysis data cut off (11 February 2019) could therefore be potentially subject to attrition bias as they do not consider the overall response rate in the whole trial population. Response analysis at the first Addendum (data cut off 15 August 2019) was based on the FAS.
- Due to the open-label nature of the trial, assessment of subjective outcomes such as quality of life (QoL) and some treatment-related adverse events (TRAEs) may be biased. Investigator and patient treatment decisions may have been influenced as they were aware of the therapy to which they were assigned. This potential for bias may have resulted in differences in study discontinuation rates which were higher in the control arm (59.3%)<sup>7</sup> than the triplet arm (41.5%)<sup>7</sup> and doublet arm (44.5%)<sup>7</sup>.
- The control arm consisted of investigator's choice of either cetuximab + irinotecan or cetuximab + FOLFIRI. As the dose of irinotecan in both regimens was the same (i.e. the difference between the regimens was the addition of 5FU + FA), investigator's choice of one regimen over the other may have biased clinical outcomes, as well as adverse events.

#### Comparative safety of the proposed test

The Commentary noted that the submission did not provide direct evidence of the clinical sensitivity/specificity and clinical positive/negative values of other testing methodologies against the evidentiary standard for the *BRAF* V600E variant. Thus, it did not directly inform the potential harm from treating a false-negative patient and the benefit forgone of not treating a false-negative patient. A sensitivity analysis conducted by the evaluation included an estimation of test accuracy in clinical practice compared to the evidentiary standard in the economic model. This increased the ICER by 5.3%.

#### Comparative safety of the proposed medicine

A similar proportion of patients on encorafenib + cetuximab compared with control arm in BEACON experienced adverse events (AEs; 98.1% vs 98.4%, respectively), but fewer Grade  $\geq 3$  AEs (57.4% vs 64.2%). Fewer patients on encorafenib + cetuximab experienced treatment related adverse effects (TRAEs) and even fewer Grade  $\geq 3$  TRAEs. The difference in Grade  $\geq 3$  TRAEs was statistically significant. The incidence of serious AEs (SAEs) and Grade  $\geq 3$  SAEs was similar between the encorafenib + cetuximab and control arms. However, treatment related SAEs and Grade  $\geq 3$  SAEs were lower in the encorafenib + cetuximab arm compared to the control arm.

The time to onset of the first Grade  $\geq 3$  AE was 4.73 months (95% CI: 3.94, 6.44) in the encorafenib + cetuximab arm and 1.41 months (95% CI: 1.08, 2.07) in the control arm. The main AEs of all Grades and Grade  $\geq 3$  that were statistically significantly different are

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<sup>7</sup> Proportion of patients discontinuing treatment: manuscript in preparation. To be submitted Q4 2021 to ESMO Open

presented in Table 5. The Commentary noted that no individual Grade  $\geq 3$  AEs occurred in statistically significantly more patients in the encorafenib + cetuximab arm compared to the control arm.

Eight patients in both arms experienced AEs resulting in on treatment deaths. In the encorafenib + cetuximab arm the causes of death included intestinal obstruction (2 patients) and aspiration (2 patients), large intestine perforation, cardio-respiratory arrest, gastrointestinal haemorrhage, and sepsis. In the control arm, the causes of death included anaphylactic reaction, cardio-respiratory arrest, cerebral ischemia, lung infection, peritonitis, pneumocystic jirovecii pneumonia, respiratory failure and subileus. The Commentary considered that the difference between Grade  $\geq 3$  diarrhoea and neutropenia between the two treatment arms was clinically relevant.

**Table 5 Summary of AEs occurring in  $\geq 10\%$  of patients or Grade  $\geq 3$  AEs ( $\geq 5\%$  in any treatment arm) of BEACON that were statistically significant (Safety Population)**

| n (%)                      | ENCO + CEUTX<br>(N = 216) |                | CONTROL <sup>a</sup><br>(N = 193) |                | All Grades                           |                                       | Grade $\geq 3$                     |                                       |
|----------------------------|---------------------------|----------------|-----------------------------------|----------------|--------------------------------------|---------------------------------------|------------------------------------|---------------------------------------|
|                            | All Grades                | Grade $\geq 3$ | All Grades                        | Grade $\geq 3$ | RR (95% CI) <sup>b</sup>             | RD (95%CI) <sup>b</sup>               | RR (95% CI) <sup>b</sup>           | RD (95%CI) <sup>b</sup>               |
| Any AE                     | 212 (98.1)                | 124 (57.4)     | 190 (98.4)                        | 124 (64.2)     | 1.00<br>(0.97, 1.02)                 | 0.00<br>(-0.03, 0.02)                 | 0.89<br>(0.76, 1.04)               | -0.07<br>(-0.16, 0.03)                |
| Diarrhoea                  | 83 (38.4)                 | 6 (2.8)        | 94 (48.7)                         | 20 (10.4)      | <b>0.79</b><br><b>(0.63, 0.99)</b>   | <b>-0.10</b><br><b>(-0.20, -0.01)</b> | <b>0.27</b><br><b>(0.11, 0.65)</b> | <b>-0.08</b><br><b>(-0.12, -0.03)</b> |
| Dermatitis acneiform       | 65 (30.1)                 | 1 (0.5)        | 77 (39.9)                         | 5 (2.6)        | <b>0.75</b><br><b>(0.58, 0.99)</b>   | <b>-0.10</b><br><b>(-0.19, -0.01)</b> | 0.18<br>(0.02, 1.52)               | -0.02<br>(-0.05, 0.00)                |
| Arthralgia                 | 49 (22.7)                 | 3 (1.4)        | 3 (1.6)                           | 0 (0)          | <b>14.59</b><br><b>(4.62, 46.07)</b> | <b>0.21</b><br><b>(0.15, 0.27)</b>    | NE                                 | 0.01<br>(0.00, 0.03)                  |
| Headache                   | 43 (19.9)                 | 0 (0)          | 5 (2.6)                           | 0 (0)          | <b>7.68</b><br><b>(3.11, 19.00)</b>  | <b>0.17</b><br><b>(0.12, 0.23)</b>    | NE                                 | 0.00<br>(0.00, 0.00)                  |
| Myalgia                    | 33 (15.3)                 | 1 (0.5)        | 4 (2.1)                           | 0 (0)          | <b>7.37</b><br><b>(2.66, 20.43)</b>  | <b>0.13</b><br><b>(0.08, 0.18)</b>    | NE                                 | 0.00<br>(0.00, 0.01)                  |
| Musculoskeletal pain       | 29 (13.4)                 | 0 (0)          | 5 (2.6)                           | 0 (0)          | <b>5.18</b><br><b>(2.05, 13.12)</b>  | <b>0.11</b><br><b>(0.06, 0.16)</b>    | NE                                 | 0.00<br>(0.00, 0.00)                  |
| Pain in extremity          | 25 (11.6)                 | 0 (0)          | 2 (1.0)                           | 0 (0)          | <b>11.17</b><br><b>(2.68, 46.54)</b> | <b>0.11</b><br><b>(0.06, 0.15)</b>    | NE                                 | 0.00<br>(0.00, 0.00)                  |
| Pruritus                   | 24 (11.1)                 | 0 (0)          | 10 (5.2)                          | 0 (0)          | <b>2.14</b><br><b>(1.05, 4.37)</b>   | <b>0.06</b><br><b>(0.01, 0.11)</b>    | NE                                 | 0.00<br>(0.00, 0.00)                  |
| Stomatitis <sup>c</sup>    | 13 (6.0)                  | 0 (0)          | 45 (23.3)                         | 4 (2.1)        | <b>0.26</b><br><b>(0.14, 0.46)</b>   | <b>-0.17</b><br><b>(-0.24, -0.11)</b> | NE                                 | -0.02<br>(-0.04, 0.00)                |
| Hypokalaemia               | 13 (6.0)                  | 2 (0.9)        | 27 (14.0)                         | 6 (3.1)        | <b>0.43</b><br><b>(0.23, 0.81)</b>   | <b>-0.08</b><br><b>(-0.14, -0.02)</b> | 0.30<br>(0.06, 1.46)               | -0.02<br>(-0.05, 0.01)                |
| Alopecia                   | 9 (4.2)                   | 0 (0)          | 21 (10.9)                         | 0 (0)          | <b>0.38</b><br><b>(0.18, 0.82)</b>   | <b>-0.07</b><br><b>(-0.12, -0.02)</b> | NE                                 | 0.00<br>(0.00, 0.00)                  |
| Neutropenia                | 3 (1.4)                   | 2 (0.9)        | 36 (18.7)                         | 20 (10.4)      | <b>0.07</b><br><b>(0.02, 0.24)</b>   | <b>-0.17</b><br><b>(-0.23, -0.12)</b> | <b>0.09</b><br><b>(0.02, 0.38)</b> | <b>-0.09</b><br><b>(-0.14, -0.05)</b> |
| Neutrophil count decreased | 1 (0.5)                   | 1 (0.5)        | 21 (10.9)                         | 16 (8.3)       | <b>0.04</b><br><b>(0.01, 0.31)</b>   | <b>-0.10</b><br><b>(-0.15, -0.06)</b> | <b>0.06</b><br><b>(0.01, 0.42)</b> | <b>-0.08</b><br><b>(-0.12, -0.04)</b> |

Notes: **Bold** text indicates a statistically significant difference.

<sup>a</sup> Control arm = investigator's choice of irinotecan + cetuximab or FOLFIRI + cetuximab

<sup>b</sup> RD and RR was calculated during the evaluation

<sup>c</sup> added during evaluation

Abbreviations: AE = adverse event; CI = confidence interval; CETUX = cetuximab; ENCO = encorafenib; n = number of participants reporting data; N = total participants in group; NE = not estimable; RD = risk difference; RR = relative risk

Source: Table 2-94, pp195 of the submission

## 11. Comparative effectiveness

### *Predictive evidence*

The submission did not present evidence of the treatment effect of encorafenib + cetuximab for patients who were *BRAF* V600E positive versus patients who were not *BRAF* V600E

positive. Thus, the Commentary considered that an estimate of the variation in treatment effect of encorafenib due to *BRAF* V600E testing could not be established from the evidence presented by the submission and so acceptance of the predictive value of the test would rely on a biological plausibility argument supported by some preclinical data. The pre-MSAC response considered that the treatment effect of encorafenib + cetuximab in patients who are *BRAF* V600E negative was redundant as the drug combination was developed specifically to address the unmet need in the *BRAF* V600E variant population.

### *Prognostic evidence*

The submission identified 20 studies for qualitative analysis, comprising 2 systematic reviews and 18 individual studies (1 prospective cohort and 17 retrospective cohort studies) providing evidence of the prognostic value of the *BRAF* V600E variant. The submission relied on the results from the 18 individual studies, where potential confounders were investigated in a multivariate analyses, or a combination of univariate and multivariate analyses, to support the claim that the *BRAF* V600E variant in mCRC is independently associated with a poorer prognosis than mCRC without the *BRAF* V600E variant. The submission nominated the prospective study as the primary evidence due to its higher level of evidence and the remaining retrospective studies as supportive evidence. The two identified meta-analyses were not used to establish a clinical claim because they did not limit their analysis to studies that adjusted for potential confounding. The Commentary considered that this was reasonable.

The Commentary considered that the evidence provided by the submission from the 18 studies demonstrated a prognostic association between the *BRAF* V600E variant and an increased risk of mortality and progression, noting the differences in study design, patient population, *BRAF* V600E testing methods and assessment of potential confounders. In the prospective study, the *BRAF* V600E variant was a strong independent negative predictor of overall (cancer-specific) survival in patients with mCRC, HR = 4.24 (95% CI: 1.77, 10.2), p=0.001. In the retrospective studies, the *BRAF* V600E variant was a strong independent negative predictor of non-cancer-specific overall survival, HRs ranged from 1.62 to 200 where analysis was limited to assessment of the prognostic value of *BRAF* V600E status.

### *Comparative analytical performance*

No reference standard was presented for the detection of the *BRAF* V600E variant in either the submission or the ratified PICO confirmation. The Commentary considered that this was reasonable. However, the Commentary highlighted that no justification was provided by the submission to support the claim of the lack of a reference standard for *BRAF* V600E testing.

The RT-PCR-CDx test was nominated by the submission as the evidentiary standard. The Commentary noted that although the definition of the evidentiary standard can only be met by the RT-PCR-CTA, used in BEACON, the submission justified its choice by conducting a bridging study to confirm the concordance between RT-PCR-CDx and RT-PCR-CTA in 1449 patients of 1677 screened for inclusion in the BEACON trial.

In BEACON, two methods for identifying the *BRAF* V600E variant were allowed: (i) local testing via next-generation sequencing (NGS) - or PCR-based methods (LDT), or (ii) in the absence of local testing, central testing via pyrosequencing using RT-PCR-CTA. All patients enrolled via LDT were to have their *BRAF* V600E status confirmed via RT-PCR-CTA within 30 days; however, patients who were LDT positive/RT-PCR-CTA negative were allowed to remain in the study at the discretion of the investigator.

The bridging study using the BEACON population was conducted to assess concordance between the RT-PCR-CTA and the RT-PCR-CDx. It demonstrated high concordance between RT-PCR-CDx and CTA, OPA = 99.9% (95% CI: 99.2%, 100%); PPA = 99.6% (95% CI: 97.9%, 100%) and 100% (95% CI: 98.6%, 100%); NPA = 100% (95% CI: 99.1%, 100%) and 99.8% (95% CI: 98.7%, 100%) when RT-PCR-CDx and RT-PCR-CTA were used as reference methods respectively.

The submission also presented comparative OS results across the BEACON population according to these two testing methodologies. When RT-PCR-CTA was used to confirm *BRAF* V600E status, the OS for encorafenib + cetuximab compared to control was HR = 0.59 (95% CI 0.45, 0.79) whilst when RT-PCR-CDx was used the HR = 0.55 (95% CI 0.41, 0.74). Based on these results, the submission claimed that, regardless of the testing methodology used, encorafenib based therapy resulted in superior efficacy in terms of OS compared with control, and that the RT-PCR-CDx test can be used as an evidentiary standard for the submission. The Commentary concluded that the submission has provided sufficient evidence to confirm that using the RT-PCR-CDx would classify very few patients differently than RT-PCR-CTA. The pre-MSAC response reiterated that the bridging study supported the high level of concordance between the RT-PCR-CTA and RT-PCR-CDx test and that any differential classification did not impact on the hazard ratio for overall survival.

The submission claimed that, since there is no reference standard for *BRAF* V600E testing, a variety of testing methods can be used in practice to confirm *BRAF* V600E status of mCRC patients. A desktop research study conducted by the submission showed that *BRAF* testing currently conducted in Australia for patients with mCRC is mostly part of a somatic gene panel approach. This was confirmed by a survey of Australian pathologists who stated that the most commonly used methodology is NGS and mass spectroscopy (MS).

To support the claim that the identification of the *BRAF* V600E variant in mCRC can be reliably carried out using a variety of testing methods, the accuracy and performance of these tests was compared against the nominated evidentiary standard where possible, and against each other where it was not. A summary of the results of the assessment of concordance of *BRAF* V600E testing between various possible comparators and reference tests in the included concordance studies is presented in Table 6. The measures of test concordance calculated by the submission were OPA, PPA and NPA. While the Commentary considered the presentation of concordance data was reasonable, the extent of misallocation of patients to treatment and the corresponding potential harms due to false positives or false negatives remains uncertain.

**Table 6 Summary of concordance results**

| Comparator test                            | OPA   | PPA   | NPA   | Source         |
|--|-------|-------|-------|----------------|
| <b>Tests compared to RT-PCR-CDx</b>        |       |       |       |                |
| Sanger sequencing                          | 95.2% | 90.6% | 100%  | FDA 2020       |
| Multiplex (RASKET-B)                       | 99.7% | 100%  | 99.6% | Taniguchi 2018 |
| RT-PCR (cobas)                             | 98.1% | 75.8% | 99.3% | Santos 2017    |
| <b>Tests compared to Sanger sequencing</b> |       |       |       |                |
| RT-PCR (AD)                                | 99.2% | 94.1% | 99.4% | Roma 2016      |
| RT-PCR (cobas)                             | 99.1% | 100%  | 98.9% | Lasota 2014    |
| RT-PCR (AS)                                | 100%  | 100%  | 100%  | Lasota 2014    |
| qPCR                                       | 100%  | 100%  | 100%  | Lasota 2014    |
| NGS (ion Torrent)                          | 100%  | 100%  | 100%  | Malapelle 2015 |
| HRM (LightMix)                             | 99.0% | 100%  | 98.9% | Løes 2015      |
| Mass spectrometry (MassArray)              | 100%  | 100%  | 100%  | Arcila 2011    |
| <b>Tests compared to dPCR</b>              |       |       |       |                |
| RT-PCR (cobas)                             | 99.0% | 83.3% | 99.8% | Santos 2017    |
| <b>Tests compared to qPCR</b>              |       |       |       |                |
| dPCR                                       | 100%  | 100%  | 100%  | Azuara 2016    |
| NGS (Ion Torrent)                          | 100%  | 100%  | 100%  | D'Haene 2015   |
| <b>Tests compared to RT-PCR (cobas)</b>    |       |       |       |                |
| RT-PCR (Idylla)                            | 99.0% | 100%  | 98.6% | Colling 2016   |
| <b>Tests compared to traditional PCR</b>   |       |       |       |                |
| WTB-PCR                                    | 94.0% | 100%  | 93.3% | Chen 2014      |
| <b>Tests compared to direct sequencing</b> |       |       |       |                |
| Multiplex (RASKET-B)                       | 100%  | 100%  | 100%  | Taniguchi 2018 |
| HRM  | 94.8% | 87.5% | 95.7% | Carbonell 2011 |
| <b>Tests compared to TaqMan</b>            |       |       |       |                |
| HRM  | 95.9% | 84.2% | 97.4% | Carbonell 2011 |
| <b>Tests compared to NGS</b>               |       |       |       |                |
| RT-PCR (Idylla)                            | 100%  | 100%  | 100%  | Colling 2017   |
| <b>Tests compared to mass spectrometry</b> |       |       |       |                |
| RT-PCR (Idylla)                            | 100%  | 100%  | 100%  | Johnston 2018  |
| <b>Tests compared to HRM-sequencing</b>    |       |       |       |                |
| Microarray                                 | 100%  | 100%  | 100%  | Galbiati 2013  |

Abbreviations: AS-PCR = allele-specific polymerase chain reaction; CDx = companion diagnostic; CTA = computed tomography angiography; dPCR = digital polymerase chain reaction; HRM = high resolution melting; MA = microarray; MP = multiplex; MS = mass spectrometry; NGS = next-generation sequencing; NPA = negative percent agreement OPA = overall percent agreement; PCR = polymerase chain reaction; PPA = positive percent agreement; PS = pyrosequencing; qPCR = real-time polymerase chain reaction; RT-PCR = real-time polymerase chain reaction; SS = Sanger sequencing; WTB = wild-type blocking.

Source: Table 2-32, p117 of the submission.

Concordance between testing methods was high, with OPA ranging between 94% and 100%, PPA ranging from 76% to 100% and NPA ranging from 93% to 100%. The discordance between these tests ranged from 0% to 6% (based on OPA). The submission noted that of relevance to the Australian setting, the concordance between NGS and RT-PCR, qPCR and Sanger sequencing was 100%, and between MS and RT-PCR and Sanger sequencing was 100%, noting NGS and MS are the most commonly used in Australia. Discordance between

RT-PCR-CDx and other testing methodologies ranged from 5% (based on OPA), when compared to Sanger Sequencing and 0.3% when compared with Multiplex.

Based on the concordance results between different methods of testing for *BRAF* V600E, the submission concluded that the *BRAF* V600E variant can be reliably identified in mCRC using different testing methodologies, and that the methodologies currently being used in Australia are likely to identify the same patient group as that included in BEACON. The Commentary considered that this conclusion was reasonable and was supported by the evidence provided in the submission.

The Commentary noted that the economic model did not include the incremental cost for *BRAF* V600E testing or the implications of test accuracy. While discordance between the testing methodologies used in Australia and the test used in BEACON is likely to be low, inclusion of test accuracy in the economic model would have been informative. Based on the concordance results presented in Table 6, the evaluation conducted a sensitivity analysis assuming a discordance of 5% between the test results obtained in practice and the primary clinical evidence. This had a small impact (5.3% increase) on the results of the economic evaluation.

#### *Prevalence*

The submission stated that approximately 10% of individuals with mCRC have the *BRAF* V600E variant. Detailed estimates of the number of Australian patients with mCRC likely to have *BRAF* V600E were based on data from the AIHW and the literature. Overall, the Commentary considered the approach used by the submission to estimate patients likely to have a *BRAF* V600E variant and be eligible for treatment with encorafenib + cetuximab was consistent with the TGA indication, the PBS listing, the clinical management algorithm and the proposed population.

#### *Change in management in practice*

The proposed change in management for the requested population for *BRAF* V600E testing would be to initiate encorafenib for those patients who have a *BRAF* V600E variant and who have received prior systemic therapy.

There is no change in clinical management for mCRC patients who do not test positive to *BRAF* V600E as per the current and proposed clinical management algorithms.

#### *Claim of codependence*

The submission stated that *BRAF* V600E positive mCRC is a distinct subtype of mCRC that has poor prognosis and has no targeted therapies currently available. To date, this patient group has been treated with the standard of care regimens used for patients with *RAS* wild-type mCRC. In Australia, EGFR treatments such as cetuximab are used in the *BRAF* V600E positive population, being indicated within *RAS* wild type.

*RAS* testing, currently undertaken via MBS item 73338, uses a somatic gene panel approach, which the submission claimed already routinely includes a *BRAF* V600E test. For the PBAC component, the submission requested the listing of encorafenib in combination with an existing PBS-listed EGFR inhibitor, such as cetuximab, for mCRC stage IV patients who have the *BRAF* V600E variant and who have received prior systemic therapy for mCRC.

The proposed listings are intended to meet an unmet need for the specific treatment of *BRAF* V600E positive mCRC patients that improves their overall survival. The key factors presented in the submission for the rationale for the MBS and PBS listings were:

- to guide the use of encorafenib doublet therapy (consisting of encorafenib and an EGFR inhibitor, such as cetuximab) as well as to provide important mCRC prognostic information
- statistically and clinically significant improvements in overall survival (OS), overall response rate (ORR), progression-free survival (PFS), with manageable tolerability and sustained quality of life (QoL), compared to chemotherapy + cetuximab.

The submission did not present evidence on the treatment effect of encorafenib + cetuximab for patients who were *BRAF* V600E positive versus patients who were not *BRAF* V600E positive. Thus, the Commentary noted an estimate of the variation in this treatment effect due to *BRAF* V600E positivity could not be established from the evidence presented and so acceptance of the predictive value of the test primarily relies on a biological plausibility argument.

### Clinical claim

The ADAR claimed that *BRAF* V600E variant testing methods likely to be used in Australia are concordant. The Commentary considered this reasonable and was supported by the evidence provided in the submission.

## 12. Economic evaluation

The submission presented a cost-effectiveness analysis comparing encorafenib + cetuximab with FOLFIRI/Ir + cetuximab based on findings from BEACON. This was consistent with the submission’s claim of superiority for encorafenib + cetuximab in terms of effectiveness compared to FOLFIRI + cetuximab or irinotecan + cetuximab, with a manageable tolerability profile and superior in terms of safety compared to FOLFIRI + cetuximab or irinotecan + cetuximab.

The analysis was structured as a partitioned survival model. Entry into the model was at the point of primary treatment and not at the point of testing. The submission stated that no incremental cost for *BRAF* V600E testing was applied in the economic model as it is currently routinely performed and reported alongside *RAS* status as an important prognostic tool. Thus, the submission assumed that the treatment initiation cost would be equal to that of the main comparator, since such testing is required for treatment with cetuximab. The Commentary noted that inclusion of test accuracy in the economic model would have been informative. The evaluation included a sensitivity analysis assuming discordance between the test results obtained in practice and the evidentiary standard was 5%. The results of the sensitivity analysis showed that this had a small impact on the ICER (5.3% increase).

The submission did not propose alternate funding scenarios with regards to the MBS item 73338. The base case incremental cost effectiveness ratio (ICER) presented in the submission is shown in Table 7.

**Table 7 Base case results of the economic evaluation**

|                      | Incremental cost | Incremental QALY | ICER                    |
|----------------------|------------------|------------------|-------------------------|
| Submission base case | \$redacted       | 0.34             | \$redacted <sup>1</sup> |

Abbreviations: ICER = incremental cost effectiveness ratio; QALY = quality adjusted life years

Source: Table MSAC.9, p13 of the Commentary.

The redacted value corresponds to the following range:

<sup>1</sup> \$75,000 to < \$95,000/QALY gained

### 13. Financial/budgetary impacts

The submission assumed that there would be no additional cost associated with the MBS listing of *BRAF* V600E testing as it is currently routinely performed and reported alongside *RAS* status (for MBS item 73338) as an important prognostic tool. The Commentary considered that this was reasonable.

The financial impact associated with the use of other MBS items (MBS items 105, 82200, 36, 63001, 56001, 56341, and 65070) likely to be affected by the listing of encorafenib is presented in Table 8. The use of these items was anticipated to increase and was consistent with MBS services applied in the economic model. Details of the estimation of the number of patients likely to receive encorafenib on the PBS is presented in the ESCs advice to the PBAC.

**Table 8 Estimated use and financial implications of PBS listing of encorafenib to the MBS**

|  | Year 1<br>(2022)              | Year 2                        | Year 3                        | Year 4                        | Year 5                        | Year 6                        |
|--|-------------------------------|-------------------------------|-------------------------------|-------------------------------|-------------------------------|-------------------------------|
| <b>Estimated extent of use of encorafenib</b>  |                               |                               |                               |                               |                               |                               |
| Number of patients (incident cases) with <i>BRAF</i> V600E variant   | redacted <sup>1</sup>         |
| Number of patients likely to receive encorafenib   | redacted <sup>1</sup>         |
| <b>Estimated financial implications of <i>BRAF</i> V600E testing to the MBS</b>  |                               |                               |                               |                               |                               |                               |
| Increased cost due to change in MBS items for PBS/RPBS beneficiaries   | \$redacted <sup>2</sup>       |
| Decrease cost due to change in MBS items for PBS/RPBS beneficiaries  | \$redacted <sup>2</sup>       |
| Net cost to the MBS budget   | \$redacted <sup>2</sup>       |
| <b>Estimated financial implications for other MBS items (likely to be affected by the PBS listing of encorafenib) to the MBS</b> |                               |                               |                               |                               |                               |                               |
| Increased cost due to change in MBS items for PBS/RPBS beneficiaries   | <i>\$redacted<sup>2</sup></i> | <i>\$redacted<sup>2</sup></i> | <i>\$redacted<sup>2</sup></i> | <i>\$redacted<sup>2</sup></i> | <i>\$redacted<sup>2</sup></i> | <i>\$redacted<sup>2</sup></i> |
| Decrease cost due to change in MBS items for PBS/RPBS beneficiaries  | <i>\$redacted<sup>2</sup></i> | <i>\$redacted<sup>2</sup></i> | <i>\$redacted<sup>2</sup></i> | <i>\$redacted<sup>2</sup></i> | <i>\$redacted<sup>2</sup></i> | <i>\$redacted<sup>2</sup></i> |
| Net cost to the MBS budget   | <i>\$redacted<sup>2</sup></i> | <i>\$redacted<sup>2</sup></i> | <i>\$redacted<sup>2</sup></i> | <i>\$redacted<sup>2</sup></i> | <i>\$redacted<sup>2</sup></i> | <i>\$redacted<sup>2</sup></i> |
| <b>Net financial implications</b>  |                               |                               |                               |                               |                               |                               |
| Net cost to MBS  | <b>\$redacted<sup>2</sup></b> | <b>\$redacted<sup>2</sup></b> | <b>\$redacted<sup>2</sup></b> | <b>\$redacted<sup>2</sup></b> | <b>\$redacted<sup>2</sup></b> | <b>\$redacted<sup>2</sup></b> |

Note: Costs in italics were updated based on MBS item fees from July 2020

Abbreviations: MBS = Medical Benefit Scheme; PBS = Pharmaceutical Benefits Scheme; RPBS = Repatriation Pharmaceutical Benefits Scheme.

Source: Table 4-5, p274 and Table 4-23, p285 of the submission.

The redacted values correspond to the following ranges:

<sup>1</sup> < 500

<sup>2</sup> \$0 to < \$10 million

## 14. Key issues from ESCs for MSAC

| ESCs key issue                        | ESCs advice to MSAC   |
|---------------------------------------|---|
| Concordance with evidentiary standard | The ESCs considered the evidence presented showed high concordance between testing methods and the submission's proposed evidentiary standard – the theascreen® real time polymerase chain reaction companion diagnostic (RT-PCR-CDx). The ESCs noted that the theascreen® RT-PCR-CDx was not technically the evidentiary standard as it was not used to identify <i>BRAF</i> V600E variants in the BEACON trial. However the bridging study presented in the submission demonstrated that the theascreen® RT-PCR-CDx test classified very few patients differently to the test used in the clinical trial. |
| Codependency                          | The ESCs noted the rationale for codependency was based on biological plausibility as there was no direct evidence that that <i>BRAF</i> V600E status is a treatment effect modifier. The ESCs considered it was reasonable to assume there would be minimal effect for <i>BRAF</i> wild-type tumours based on biological plausibility and some preclinical data.   |

### ESCs discussion

The ESCs noted that the submission sought to include testing for the V600E pathogenic genetic variant of the *BRAF* gene into the existing MBS item 73338 (*RAS* testing in metastatic colorectal cancer (mCRC)) to determine eligibility for treatment with encorafenib in combination with an epidermal growth factor receptor (EGFR) inhibitor such as cetuximab. The ESCs noted that no change in the existing MBS fee was proposed as the submission claimed *BRAF* V600E testing was already conducted alongside *RAS* testing using existing panel testing approaches.

From a consumer perspective, the ESCs noted that access to testing may be more difficult for patients in rural and remote areas and a lack of data from patient-reported outcome and experience measures. The ESCs also noted that the cost of genetic testing is expected to decrease over time and it may be appropriate to review MBS fees in the future.

The ESCs noted that the comparator for *BRAF* V600 testing was is MBS item 73338 with its current item descriptor (*RAS* testing only). The comparator for encorafenib + EGFR inhibitor (cetuximab) was FOLFIRI (folinic acid/fluorouracil/irinotecan) + an EGFR (cetuximab). The ESCs noted that FOLFIRI and cetuximab is generally not used for patients with the pathogenic *BRAF* V600E variant.

The ESCs noted that the rationale for codependency was based on biological plausibility as the BEACON trial only enrolled patients with the V600E pathogenic variant of the *BRAF* gene. The ESCs noted that biological plausibility was supported by preclinical studies showing a combined inhibition of BRAF and EGFR receptors results in a synergistic inhibition of tumour growth in *BRAF* V600E human tissue xenograft models grown in nude mice.

The ESCs noted there that was consistent evidence showing that patients with a *BRAF* V600E variant have a poorer prognosis than patients without a *BRAF* V600 variant. The ESCs noted that these studies of prognosis varied in study design, patient population, testing methods and assessment of potential confounders.

The ESCs noted that no reference standard was identified. MSAC noted that Sanger sequencing with confirmatory pyrosequencing was proposed as the reference standard testing of all *BRAF* V600 variants (rather than *BRAF* V600E) in melanoma (p3, [Application 1172 Public Summary Document \[PSD\]](#)). The ESCs noted that the clinical claims were based on the evidentiary standard.

The ESCs noted that patients entering the trial could undergo *BRAF* V600E testing using either the central test using the theascreen® pyrosequencing test (RT-PCR-CTA) or local testing that was next generation sequencing (NGS)-based or polymerase chain reaction (PCR)-based. Local testing was confirmed using the central test. The ESCs noted that the submission presented a bridging study that compared the central test with the submission's proposed evidentiary standard theascreen® real time (RT) polymerase chain reaction (PCR) companion diagnostic (RT-PCR-CDx) which contains software design changes to the central test (RT-PCR-CTA). The ESCs noted the Commentary did not accept the theascreen® RT-PCR-CDx test as the evidentiary standard as it was not the test used to identify patients with the *BRAF* V600E variant in the trial. The ESCs agreed that this was technically true but agreed with the pre-ESCs response that the theascreen® RT-PCR-CDx test classified very few patients differently to the RT-PCR-CTA.

The ESCs noted that the submission had presented analytical performance studies that reported concordance between RT-PCR-CDx and other test options available in Australia (Table 6). The ESCs highlighted the nested case control study reported by the FDA (part of the BEACON bridging study), which used samples consecutively enrolled on the date of sampling to minimise bias. This study reported higher proportions of indeterminate results with Sanger sequencing than with RT-PCR-CDx (of the 600 included samples, 79 (13%) were indeterminate with RT-PCR-CDx and 136 samples (23%) were indeterminate by Sanger sequencing), and lower positivity rate with Sanger sequencing than RT-PCR-CDx (of the 192 positive samples identified by Sanger sequencing, all were identified as positive by RT-PCR-CDx; an additional 20 samples identified as positive using the RT-PCR-CDx were identified as having no pathogenic variant on Sanger sequencing). This implies that Sanger sequencing may be more conservative in identifying the pathogenic variant than RT-PCR-CDx, and than the evidentiary standard RT-PCR-CTA. However, the ESCs noted that overall positive agreement across this and the other studies was greater than 95%. The ESCs further noted that *BRAF* V600E testing is already reimbursed for patients with melanoma and agreed with the pre-ESCs response that that testing should not be limited to a particular methodology. The ESCs also considered that testing may be done sequentially, with *BRAF* V600E testing only performed in patients where *RAS* pathogenic variants have not been identified, but it would not be necessary to require this. The ESCs did not express a view on whether the item should also be restricted to once per cancer diagnosis.

The ESCs noted the National Pathology Accreditation Advisory Council advice that *BRAF* V600E testing is already established in a number of laboratories in Australia and that an external quality assurance program is available through the Royal College of Pathologists of Australasia Quality Assurance Program P/L.

The ESCs noted that although the BEACON trial compared the efficacy of encorafenib with cetuximab, it may be reasonable to patients to have to option to use encorafenib in combination with panitumumab. The ESCs noted the absolute median difference in overall survival of redacted<sup>8</sup> months was small.

The ESCs noted that the economic evaluation was a partitioned survival model where entry into the model was at the point of primary treatment and not at the point of testing.

The ESCs noted that a sensitivity analysis performed by the Commentary showed that test discordance of 5% had little impact on the ICER. The ESCs considered that the assumption of 5% discordance was at the higher end of likely values based on the clinical evidence and

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<sup>8</sup> OS data cut off May 2020: manuscript in preparation. To be submitted Q3 2021 to BMJ Open

therefore represented worst-case assumption. Overall, the ESCs considered that there were no significant economic issues for MSAC's consideration.

The ESCs noted that there is no anticipated financial impact to the MBS as there is no proposed change to the fee and the proposed change is unlikely to affect uptake of the item. The ESCs noted the estimated reduction in treatment regimens replaced may not be appropriate and that any changes to the estimates of utilisation of these regimens on the PBS would need to be reflected in these estimates.

#### **15. Other significant factors**

Nil

#### **16. Applicant comments on MSAC's Public Summary Document**

Pierre Fabre welcome the opportunity to work with MSAC and PBAC to enable reimbursed access to BRAF V600 testing and Braftovi (encorafenib) for Australian patients with BRAF V600E variant metastatic colorectal cancer.

#### **17. Further information on MSAC**

MSAC Terms of Reference and other information are available on the MSAC Website:  
[visit the MSAC website](#)